

PATENT  
09/990,522  
Docket 097/002

Objection to the Claims:

Claim 20 is objected to for use of the word "their" in reference to the antecedent single individual. This objection is based on the common misconception that the pronoun "their" should only be used in the plural form. In fact, the word "their" has a long and noble heritage for use in the third person singular.

*Appendix A* accompanying this response provides interesting information borrowed from a website by Henry Churchyard, and elsewhere on the internet. The information provides a large number of literary examples in which the word "their" is used in the singular form. Authority for such use is sourced from the *Merriam-Webster Dictionary*, and the *Oxford English Dictionary*.

The undersigned respectfully submits that the present wording of the claim is more concise and more elegant than the alternative choice in wording:

20. A method of preparing an individual for therapy to reconstitute his or her cellular function, comprising administering to the individual . . .

The use of the word "their" in the claim as presently worded is entirely proper. It does not affect the clarity of the claim within the requirements of 35 USC § 112 ¶ 2. The undersigned therefore wishes to exercise his prerogative to word the claim in the manner he prefers.

Withdrawal of this rejection is respectfully requested.

Rejection under 35 USC § 112 ¶ 1:

Claims 1-20 stand rejected under § 112 ¶ 1 as not being enabled by the specification to make and/or use the invention. The Office Action refers generally to the breadth of the claims, the state of the art, and the amount of guidance in the specification.

Applicant respectfully disagrees. The specification describes in considerable detail the preparation and growth of pluripotent stem cells (pp. 7 to 10), the making of therapeutic cell populations such as cardiomyocytes (pp. 10 to 12), the making of tolerizing cell populations such as mesenchymal cells (pp. 12 to 15), and the use of the cell populations to induce tolerance and effect tissue regeneration (pp. 15 to 19).

The Office Action quotes from several published articles in support of the rejection.

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- Kaufman et al. (Proc. Natl. Acad. Sci. USA 98:10716, 2001) is referred to in support of the proposition that the use of hES cell based therapies is novel, and that safety and efficacy concerns need to be addressed before human clinical trials can be initiated. It is the role of the Food and Drug Administration (not the U.S. Patent and Trademark Office) to evaluate what is needed for investigators to proceed with a human clinical trial. At any rate, the Patent Office does not require applicants to provide clinical trial data before issuing a patent on a potentially useful pharmaceutical formulation.
- Waldmann et al., Nature Med. 5:1245, 1999, and Sussman, Nature 410:640, 2001, are referred to in support of the proposition that little is known about using cells made from human pluripotent stem (pPS) cells. The Office is respectfully reminded that the Office has the burden of showing that the invention is not adequately enabled by the application<sup>1</sup>. It is insufficient just to show that the claimed inveniton has not been done before. In fact, novelty of the inveniton is a requirement of patentability under 35 USC § 102.
- Fandrich et al. (Nature Med. 8:171, 2002) is referred to in support of the proposition that embryonic stem cells are not known to survive in an allogeneic host environment. *This is one of the problems that the present invention is designed to solve.*
- Grounds et al. (J. Histochem. Cytochem. 50:589, 2002) is referred to in support of the proposition that human ES cells to cardiomyocytes occurs at a low frequency. This is not sufficient grounds for lack of enablement. The specification provides a detailed method developed at Geron Corporation for the making of high purity populations of cardiomyocytes from ES cells by using a cardiotrophic factor, separating cells of the right phenotype by density centrifugation, and then culturing the cells in a medium that further promotes the outgrowth of cardiomyocytes or their precursors. The same method is the subject of U.S. Patent Application 10/193,884 (published as US-2003-0022367-A1). These strategies

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<sup>1</sup> *In re Wright*, 27 USPQ2d 1510 (Fed. Cir. 1993). It is incumbent upon the Office to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning. *In re Marzocchi* 169 USPQ 367, 370 (CCPA 1971). [A]ny party making the assertion that a U.S. patent specification or claims fails, for one reason or another, to comply with § 112 bears the burden of persuasion in showing said lack of compliance. *Fiers v. Revel*, 25 USPQ2d 1602 (Fed. Cir. 1993). The examiner should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation. MPEP § 2164.04.

considerably enrich the proportion of hES derived cardiomyocytes in the preparation (e.g., Figure 9 of USSN 10/193,884). See also Xu et al., *Circ Res.* 91:501, 2002.

- Bachar-Lustig et al., *Blood* 94:3212, 1999) is referred to in support of the proposition that it may be difficult to harvest sufficient bone marrow progenitor cells in humans at megadoses required for overcoming transplantation barriers. This is another limitation of previous technology *which is solved by this invention*. Embryonic stem cells can be grown up to any volume desired (Carpenter et al., *Cloning Stem Cells*, 5:79, 2003). Using hES cells as a source of the toleragenic cell population *rather than human bone marrow* can provide any volume of cells that is required.

In fact, there is a good deal of work available that shows the elements needed for the invention to work in the manner described are in place as described in the application.

First of all, with respect to the use of cells for cardiac repair, there are a number of trials under way at the preclinical and clinical stage showing considerable efficacy. For example, Menasché et al recently reported results of a Phase I trial in which human patients were treated with myocytes grown from a biopsy of the patient's own thigh muscle (*J. Am. Coll. Cardiol.* 41:1078, 2003)<sup>2</sup>. The authors conclude that the therapy is safe and has therapeutic promise. You et al. (*J. Molec. Cell. Cardiol.* 35:661, 2003) reported results of an animal model in which isogenic (histocompatibility matched) fetal cardiomyocytes grafted into the ischemic heart, and were still present *after 10 months*. The transplant increased infarct wall thickness, reduced left ventricular dilation, and improved ejection fraction.

In both studies, the transplant cells were injected *directly into the heart tissue*. Someone skilled in the art reading the present application would know to tailor the administration of the therapeutic cells depending on the nature of the condition being treated. For cardiac regeneration, the skilled reader will know that direct injection is appropriate (for example, during open heart surgery), and other procedures (such as administration during angioplasty) may also be feasible. Thus, it is not necessary for the heart cells to "home" to the heart after injection into the general circulation, as suggested in the Office Action (although this option is not excluded).

<sup>2</sup> Copies of the supporting publications referred to in the following section are provided for the convenience of the Examiner in an Information Disclosure Statement being filed on the same date as this response.

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The viability of using cardiomyocytes in therapy being well established, the only remaining question raised in the Office Action is the ability of hES-derived cells to induce tolerance in accordance with the invention.

Accompanying this Response is *Appendix B*, providing data that demonstrate the toleragenic potential of hES derived cells. Example 1 describes a mixed lymphocyte reaction (MLR), in which the ability of hES cells to stimulate allogeneic responder T lymphocytes was assessed by [<sup>3</sup>H]thymidine incorporation. The data show that hES cells are not immunostimulatory, even though most mature cells (such as cardiomyocytes) provoke a strong allogeneic response under these circumstances.

Example 2 describes a three component culture, in which hES cells are combined into a standard MLR in which T lymphocytes are responding to primed allogeneic dendritic cells. The data show that the hES cells actually *suppress* the T cells from reacting against the dendritic stimulators, which otherwise provoke a strong reaction.

Example 3 describes another MLR in which the hES cells have been differentiated into cells with a precursor phenotype. The data show that the progenitor cells used in this experiment share with hES cells an ability to prevent reactivity of allogeneic cells. The combined data are consistent with the hypothesis that hES derived progenitors in general are suitable cells to induce tolerance against the histocompatibility alloantigens they express.

In this respect, hES derived toleragenic cells made according to this invention appear to have the same properties in mixed lymphocyte reactions conducted in culture as toleragenic cells obtained from bone marrow — such as mesenchymal stem cells, and hematopoietic cells of various kinds.

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Published patents and articles confirm that mesenchymal cells and hematopoietic cells can be used to enhance survival of tissue allografts. For example:

- Seung et al. (J. Clin. Invest. 112:795, 2003) did experiments treating mice with allogeneic bone marrow cells, and then applying a skin allograft. The authors concluded that robust allogeneic chimerism and central tolerance can be established in the absence of myeloablative conditioning of the transplant recipient by way of a peripheral transplantation tolerance protocol.
- U.S. Patent 6,368,636 (issued on April 9, 2002) is entitled *Mesenchymal Stem Cells for Prevention and Treatment of Immune Responses in Transplantation*. Mesenchymal stem cells obtained from bone marrow were unreactive in MLRs (Examples 1, 3, and 4), and suppressed third-party MLRs (Examples 2, 5, and 6). The mesenchymal stem cells improved the survival time of skin allografts transplanted in juvenile baboons.
- Kuhr et al. (Transplantation 73:1487, 2002) report a study in a dog model in which bone marrow stem cells were used to tolerize recipients for organ transplantation. The dogs were then given a kidney transplant from the same donor from which the stem cells were obtained. With follow-up of over 1 year, all five of the treated dogs had excellent renal function, indicating that the renal graft was still in place and functioning properly.
- Barber et al. (Transplantation 51:70, 1991) did a long-term controlled prospective clinical study with transfusion of donor-specific bone marrow in cadaveric renal allograft recipients. The patients were tolerized with bone marrow cells obtained from the same donor as the transplanted kidney. The pretreatment was found to be associated with improved survival of the allograft.
- Fontes et al. (Lancet 343:151, 1994) pretreated recipients to induce tolerance, using matched donor bone marrow cells in conjunction with transplantation of a kidney, liver, or heart allograft. All recipients were reported as well.

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- Rifle and Mousson (Transplantation 75 Suppl:3S, 2003) have written a recent review on the use of donor-derived hematopoietic cells to induce allograft tolerance in organ transplantation. Various fractions of bone marrow have been tested successfully in preclinical and clinical trials (Table 1). The authors conclude that tolerance induction in humans using donor-derived cells is a relatively safe solution that is both promising and realistic.

In summary, the information summarized in this Response confirm:

1. Cardiomyocytes are a viable therapy for heart disease;
2. hES cells and their derivatives have the properties needed in mixed lymphocyte reactions done in tissue culture to act as tolerizing cells; and
3. Tolerizing cells of the same histocompatibility type as an allograft improve survival of the allograft.

Thus, all the elements of the claimed invention should work in the manner indicated. Withdrawal of the rejection is respectfully requested.

#### Request for Interview

Applicant respectfully requests that all outstanding objections and rejections be reconsidered and withdrawn. The application is believed to be in condition for allowance, and a prompt Notice of Allowance is requested.

In the event that the Examiner determines that there are other matters to be addressed, applicant hereby requests an interview by telephone.

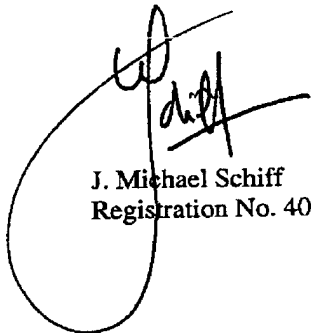
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Fees Due

Enclosed with this Amendment is authorization to charge the Deposit Account for the extension of time and the Information Disclosure Statement.

Should the Patent Office determine that a further extension of time or any other relief is required for further consideration of this application, applicant hereby petitions for such relief, and authorizes the Commissioner to charge the cost of such petitions and other fees due in connection with the filing of these papers to Deposit Account No. 07-1139, referencing the docket number indicated above.

Respectfully submitted,



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December 18, 2003

## APPENDIX A

### The singular "they"/"their"/"them"/"themselves" construction

These files contain a list of over 75 occurrences of the words "they"/"their"/"them"/"themselves" referring to a singular antecedent with indefinite or generic meaning in Jane Austen's writings (mainly in her six novels), as well as further examples of singular "their" etc. from the *Oxford English Dictionary* (OED) and elsewhere. While your high-school English teacher may have told you not to use this construction, it actually dates back to at least the 14th century, and was used by the following authors (among others) in addition to Jane Austen: Geoffrey Chaucer, Edmund Spenser, William Shakespeare, the King James Bible, *The Spectator*, Jonathan Swift, Daniel Defoe, Frances Sheridan, Oliver Goldsmith, Henry Fielding, Maria Edgeworth, Percy Shelley, Lord Byron, William Makepeace Thackeray, Sir Walter Scott, George Eliot [Mary Anne Evans], Charles Dickens, Mrs. Gaskell, Anthony Trollope, John Ruskin, Robert Louis Stevenson, Walt Whitman, George Bernard Shaw, Lewis Carroll, Oscar Wilde, Rudyard Kipling, H. G. Wells, F. Scott Fitzgerald, Edith Wharton, W. H. Auden, Lord Dunsany, George Orwell, and C. S. Lewis.



Singular "their" etc., was an accepted part of the English language before the 18th-century grammarians started making arbitrary judgements as to what is "good English" and "bad English", based on a kind of pseudo-"logic" deduced from the Latin language, that has nothing whatever to do with English. (See the 1975 journal article by Anne Bodine in the bibliography.) And even after the old-line grammarians put it under their ban, this anathematized singular "their" construction never stopped being used by English-speakers, both orally and by serious literary writers. So it's time for anyone who still thinks that singular "their" is so-called "bad grammar" to get rid of their prejudices and pedantry!

#### A brief history of singular "their" (etc.)

The following is a brief potted history of this construction:

In Old English, the masculine gender was used as the "unmarked" default for some purposes, but the problem of which pronouns to use with an indefinite singular antecedent (which can refer to both men and women) did not exist in quite the same way that it does in more recent English. This is because in Old English there was a system of arbitrary "grammatical gender", in which nouns were assigned a gender which was often independent of the biological sex (if any) of the noun's referent (as also happens in modern German, French etc.), and articles, demonstratives, and adjectives (as well as third person singular pronouns) all took on different forms according to the grammatical gender of the noun words they accompanied. It was apparently in early Middle English, with the transition to a system of "natural gender" (in which the third person singular pronouns are almost the only surviving linguistic markers of gender, and they are basically used in accordance with the biological sex of the referents of their antecedent nouns), that there arose the pronominal "generic masculine" construction as such -- in which it is only by a separate convention (somewhat isolated from regular rules of pronoun agreement) that masculine pronouns are used in sentences of the type "Everybody loves his own mother".

However, not long afterwards the "singular their" construction ("Everybody loves **their** own mother") also came into existence, and is attested starting in the late 1300's. So from the fourteenth century on, both "singular their" and the pronominal generic masculine existed in English, and were two competing solutions for the same problem.

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From then on, "singular their" was used without much inhibition (see the examples from the OED) and was not generally considered "bad grammar". It is true that starting in the 16th century, when English grammar began to be a subject of study, some rules of Latin grammar were applied to English; and that the Latin-based rules of grammatical agreement might have been seen as forbidding the English singular "their" construction -- if they were interpreted in a certain linguistically naïve way. (This may explain why certain classical-language-influenced authors, such as the translators of the King James Bible, tended to use singular "their" somewhat infrequently -- but see Phillipians 2:3.) However, the earliest specific condemnation of singular "their" that Bodine was able to find (in her 1975 article) dated only from 1795 (more than two centuries after English grammar started being taught, and at least several decades after the beginning of the 18th century "grammar boom").

So it seems that it was only in the late 18th century or early 19th century, when prescriptive grammarians started attacking singular "their" because this didn't seem to them to accord with the "logic" of the Latin language, that it began to be more or less widely taught that the construction was bad grammar. The prohibition against singular "their" then joined the other arbitrary prescriptions created from naïve analogies between English and Latin -- such as the prohibition against ending a sentence with a preposition.

But through the 19th and 20th centuries, singular "their" has still continued to be used by a number of even somewhat "literary" authors, as well as commonly in the speech of even many educated individuals.

It is interesting that almost as soon as the banning of singular "their" by grammarians and schoolteachers had gained some degree of acceptance (making many feel that the singular "their" construction was out of place in writing), some people began feeling dissatisfaction with the other alternatives which were permitted by the arbitrary edicts of prescriptive grammarians. So already in 1808/1809, noted author Samuel Taylor Coleridge seems to have rejected "generic masculine" *he* in some cases (as not being appropriately gender-neutral) -- and since he apparently did not consider singular "their" to be permissible, and probably felt that "he or she" was too cumbersome (especially in repetition), he settled on "it" as the only available solution, as discussed in the following passage:

QUÆRE -- whether we may not, *nay* ought not, to use a neutral pronoun, relative or representative, to the word "Person", where it hath been used in the sense of *homo*, *mensch*, or noun of the common gender, in order to avoid particularising man or woman, or in order to express either sex indifferently? If this be incorrect in syntax, the whole use of the word Person is lost in a number of instances, or only retained by some stiff and strange position of the words, as -- "not letting the *person* be aware *wherein offense has been given*" -- instead of -- "wherein he or she has offended". In my [judgment] both the specific intention and general *etymon* of "Person" in such sentences fully authorise the use of *it* and *which* instead of *he*, *she*, *him*, *her*, *who*, *whom*.

-- *Anima Poetæ: From the Unpublished Note-Books of Samuel Taylor Coleridge*, edited by Ernest Hartley Coleridge (1895), p. 190. ["Homo" and "mensch" are Latin and German words which mean 'man' in a general sex-neutral sense, as opposed to "vir" and "mann", which mean 'man' in the specifically masculine sense.]

Similarly, dissatisfaction with generic "he" and the other prescriptively-allowed alternatives led to proposals for neologistic English gender-neutral singular human pronoun words beginning in the mid-nineteenth century, as can be seen at Dennis Baron's "Word that Failed" page.

## Singular "their" and linguistic sexism in English

Recently, various new constructions or new words have been proposed to mitigate perceived English linguistic sexism; these are innovations, and must be evaluated as such. But singular "their" (etc.) is not an innovation, but old established good usage. So here anti-sexism and traditional English usage go hand-in-hand -- and those who object to singular "their" can find no support from history, linguistics, or the aim of inclusive language.

Already in 1894, the famed grammarian and linguist Otto Jespersen (who was decidedly not a feminist himself) wrote in his book *Progress in Language: With Special Reference to English* (§24) that "it is at times a great inconvenience to be obliged to specify the sex of the person spoken about. [...] if a personal pronoun of common gender was substituted for *he* in such a proposition as this: 'It would be interesting if each of the leading poets would tell us what he considers his best work', ladies would be spared the disparaging implication that the leading poets were all men." (so that it can hardly be claimed that a concern about such matters is only a recent outgrowth of 1970's feminism or so-called "PC" ideology).

### Conditions on the use of singular "their" etc.

Contrary to what some people apparently believe -- that as soon as speakers deviate in the slightest degree from the prescriptive rules inculcated in schools, the English language then begins to spontaneously degenerate into a chaos of incoherent mumbles -- there are actually clearly-defined patterns in the use of singular "their" etc. Such plural pronouns can only be used with a morphologically and syntactically singular antecedent when what it refers to is semantically collective and/or generic and/or indefinite and/or unknown. (A lack of knowledge about the gender of what is referred to, or an "epicene" reference to both genders or indefinitely to either, will in many cases help to make the use of singular "their" sound acceptable, by contributing to such semantic indeterminacy; however, note that unspecified gender is actually neither a necessary or sufficient condition for use of singular "their" -- see below for non-"epicene" examples of this construction.)

Where singular "their" **cannot** be used is when referring to a strongly-individualized single person about whom there is some specific information. So the following attempt at pronominal reference would fail, even if one did not know (or did not wish to reveal) the sex of "Chris": "Chris was born on February, 25th 1963, the youngest of three siblings, is 5 feet 9 inches tall with red hair, graduated from Slippery Rock college, is currently working as an accountant, has never married, and is fond of listening to jazz. They..." (This shows that singular "they"/"them"/"their" cannot be used in all cases of unknown or indefinite gender.)

These semantic factors are gradient, which is why some speakers find "their" etc. which refers back to an indefinite pronoun such as "anybody" more acceptable than cases of "their" etc. referring back to a singular concrete noun. So in the great majority of cases in Jane Austen's writings, singular "their" has indefinite pronouns or quantifier words as its antecedent; there are also a few cases of "a person", "any young person", and "any man" as the antecedent, but no cases of a more specific noun phrase as the antecedent (except perhaps one case of "any acquaintance" embedded in a parallel coordinate construction). (It is significant that in one of the two cases I have found of the generic masculine construction in Jane Austen the antecedent is "the reader", with a definite article and a concrete noun.)

➔ Go to a linguistic and logical discussion of singular their by Steven Pinker

## The singular "their" (etc.) construction in Jane Austen

"And this, too, she calls a frolic, or in her own vulgar language, fun."  
 -- Lady Delacour in Chapter IV of Maria Edgeworth's *Belinda*

Jane Austen's attitude towards singular "their" is shown by the fact that she uses it even in the narration of her novels -- it is conspicuously **not** confined to the quoted speech of vulgar and ignorant characters, in the way that certain other constructions in Jane Austen are.

For example, phrases of the type "me and..." are used as the subject of a verb only by characters such as Lydia Bennet of *Pride and Prejudice* ("Kitty and me were to spend the day there... Mrs. Forster and me are *such* friends!"; "...as we went along, Kitty and me drew up all the blinds, and pretended there was nobody in the coach", all from Chapter 39); Lucy Steele of *Sense and Sensibility* ("...my sister and me was often staying with our uncle..." from Chapter 22, and "Ann and me are to go, the latter end of January, to some relations who have been wanting us to visit them these several years" from Chapter 24); and Mrs. Elton of *Emma* ("Neither Mr. Suckling nor me had ever any patience with them; and we used sometimes to say very cutting things!", from Chapter 38). Similarly, the word "fun" is only used once by John Thorpe in *Northanger Abbey* and eight times by Lydia Bennet of *Pride and Prejudice*, and the main users of "ain't" are Nancy Steele and Mrs. Jennings of *Sense and Sensibility*.

It's also interesting that in several of the examples (they are pointed out in the list), singular "their" refers to each of several women, and so was not used to express gender-neutrality. The reason for this is that singular "their" can serve as a general way of expressing indefiniteness, which need not have anything whatever to do with gender-neutrality. So for example, Shakespeare wrote "There's not a man I meet but doth salute me / As if I were **their** well-acquainted friend" (*Comedy of Errors*, Act IV Scene 3), and in Mrs. Gaskell's 1855 novel *North and South*, a male character says "I was never aware of any young lady trying to catch me [i.e. matrimonially], nor do I believe that anyone has ever given **themselves** that useless trouble".

The total number of occurrences of singular "their" etc. found in Austen's six novels was 75, distributed as follows (see also the more detailed statistics):

- Full-length (three-volume) novels:
  - *Mansfield Park*: 24
  - *Emma*: 14
  - *Sense and Sensibility*: 12
  - *Pride and Prejudice*: 12
- "Half-length" (two-volume) novels:
  - *Northanger Abbey*: 7
  - *Persuasion*: 6

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➔ Go to List of examples of singular "their" etc. from Jane Austen's writings

➔ Go to List of examples of singular "their" etc. from the OED and elsewhere

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## Selective bibliography on singular "their", generic masculine, etc.

This is a selective condensation and rearrangement of a posting on the LINGUIST mailing list:

**Date:** Thu, 29 Apr 93 18:43:25 PDT

**From:** (Johanna Rubba)

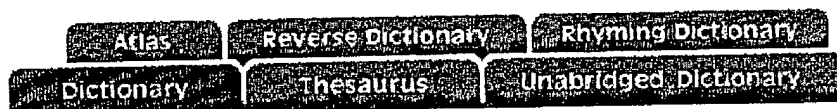
**Subject:** Summary: Language and gender

What follows is a list of references that were sent to me by various individuals on the subject of language and gender, especially the problem of 'generic' or epicene pronouns.

- Abbott, Gerry. "Unisex 'they'", *English Language Teaching Journal*, 1984. **38**, 45-48.
- Baron, Dennis. *Grammar and Gender*, Chapter 10. 1986. New Haven: Yale University Press.
- Bodine, Anne. "Androcentrism in Prescriptive Grammar: Singular 'they', Sex-indefinite 'he', and 'he or she'", *Language in Society*, 1975. **4**, 129-146.
- articles "Agreement: indefinite pronouns" and "They, their, them" in E. Ward Gilman ed. *Webster's Dictionary of English Usage*. 1989. Springfield Massachusetts: Merriam-Webster.
- Green, W. H. "Singular Pronouns and Sexual Politics", *College Composition and Communication*, 1977. **28**, 150-153.
- Hofstadter, Douglas R. "Changes in Default Words and Images, Engendered by Rising Consciousness" and "A Person Paper on Purity in Language", Chapters 7 and 8 in *Metamagical Themas: Questing for the Essence of Mind and Pattern*, 136-167. 1985. New York: Basic Books.
- Jespersen, Otto. Section 5.56 in *A Modern English Grammar on Historical Principles. Part II: Syntax, First Volume*, 137-140, addenda p. 495. 1913 (1948).
- Korsmeyer, Carolyn. "The Hidden Joke: Generic Uses of Masculine Terminology", in Mary Vetterling-Braggin ed. *Sexist Language: A Modern Philosophical Analysis*, 116-31. 1981. New Jersey: Littlefield, Adams & Co.
- Martyna, Wendy. "The Psychology of the Generic Masculine", in Sally McConnell-Ginet, Ruth Borker, and Nelly Furman, eds. *Women and Language in Literature and Society*, 69-78. 1980. New York: Praeger.
- Meyers, Miriam Watkins. "Forms of *they* with Singular Noun Phrase Antecedents", *Word*, 1993. **44** 181-191.
- Miller, Casey and Kate Swift. *Words and Women*. 1976. Garden City, New York: Anchor.
- Mühlhäusler, Peter and Rom Harré. "He, She, or It: The Enigma of Grammatical Gender", Chapter 9 in *Pronouns and People: The Linguistic Construction of Social and Personal Identity*, 229-247. 1991. Basil Blackwell.
- Newman, Michael. "Pronominal Disagreements: The Stubborn Problem of Singular Epicene Antecedents", *Language in Society*, 1992. **21**, 447-475.
- Pinker, Steven. *The Language Instinct*, 378-379. 1994. New York: W. Morrow.
- Sklar, E. S. "The Tribunal of Use: Agreement in Indefinite Constructions", *College Composition and Communication*, 1988. **39**, 410-422.
- Stanley, J. P. "Sexist Grammar", *College English*, 1978. **39**, 800-811.

(A summary on the "generic masculine" and related issues in English, with some further references, is available on-line as section 5 of the paper "Why there are so few Female Computer Scientists" by Ellen Spertus.)

# Merriam-Webster DICTIONARY

One entry found for **they**.

Main Entry: **they** ❹

Pronunciation: ' [t̬h] A

Function: *pronoun, plural in construction*

Etymology: Middle English, from Old Norse *their*, masculine plural demonstrative & personal pronoun; akin to Old English *thæt* that

Date: 13th century

**1 a** : those ones -- used as third person pronoun serving as the plural of *he*, *she*, or *it* or referring to a group of two or more individuals not all of the same sex <*they* dance well> **b** : <sup>1</sup>~~HE~~ **2** -- often used with an indefinite third person singular antecedent <everyone knew where *they* stood -- E. L. Doctorow> <nobody has to go to school if *they* don't want to -- N. Y. Times>

**2** : ~~PEOPLE~~ **2** -- used in a generic sense <as lazy as *they* come> **usage** *They* used as an indefinite subject (sense 2) is sometimes objected to on the grounds that it does not have an antecedent. Not every pronoun requires an antecedent, however. The indefinite *they* is used in all varieties of contexts and is standard.

**usage** *They*, *their*, *them*, *themselves*: English lacks a common-gender third person singular pronoun that can be used to refer to indefinite pronouns (as *everyone*, *anyone*, *someone*). Writers and speakers have supplied this lack by using the plural pronouns <and every one to rest *themselves* betake -- Shakespeare> <I would have everybody marry if *they* can do it properly -- Jane Austen> <it is too hideous for anyone in *their* senses to buy -- W. H. Auden>.

The plural pronouns have also been put to use as pronouns of indefinite number to refer to singular nouns that stand for many persons <'tis meet that some more audience than a mother, since nature makes *them* partial, should o'erhear the speech -- Shakespeare> <a person can't help *their* birth -- W. M. Thackeray> <no man goes to battle to be killed. -- But *they* do get killed -- G. B. Shaw>. The use of *they*, *their*, *them*, and *themselves* as pronouns of indefinite gender and indefinite number is well established in speech and writing, even in literary and formal contexts. This gives you the option of using the plural pronouns where you think they sound best, and of using the singular pronouns (as *he*, *she*, *he or she*, and their inflected forms) where you think they sound best.

## Examples of singular "their" from the *Oxford English Dictionary*



Everybody loves  
THEIR OED

- They

2. Often used in reference to a singular noun made universal by *every*, *any*, *no*, etc., or applicable to one of either sex (= 'he or she').

See Jespersen *Progress in Lang.* §24.

- 1526 *Pilgr. Perf.* (W. de W. 1531) 163b, Yf... a psalme scape ony persone, or a lesson, or else yt. they onyt one verse or twayne.
- 1535 FISHER *Ways perf. Relig.* ix. Wks. (1876) 383 He neuer forsaketh any creature vnlesse they before haue forsaken them selues.
- 1749 FIELDING *Tom Jones* VIII. xi, Every Body fell a laughing, as how could they help it.
- 1759 CHESTERF. *Lett.* IV. ccclv. 170 If a person is born of a gloomy temper ... they cannot help it.
- 1835 WHEWELL in *Life* (1881) 173 Nobody can deprive us of the Church, if they would.
- 1858 BAGEHOT *Lit. Stud.* (1879) II. 206 Nobody fancies for a moment that they are reading about anything beyond the pale of ordinary propriety.
- 1866 RUSKIN *Crown Wild Olives* §38 (1873) 44 Now, nobody does anything well that they cannot help doing.
- 1874 [see THEMSELVES 5].

- Them

2. Often used for 'him or her', referring to a singular person whose sex is not stated, or to *anybody*, *nobody*, *somebody*, *whoever*, etc. Cf. THEY 2.

- 1742 RICHARDSON *Pamela* III. 127 Little did I think... to make a... complaint against a Person very dear to you,... but dont let them be so proud... as to make them not care how they affront everybody else.
- 1853 MISS YONGE *Heir of Redclyffe* xlv, Nobody else... has so little to plague them.
- 1874 DASENT *Half a Life* II. 198 Whenever anyone was ill, she brewed them a drink.

- **Themselves**

5. In concord with a singular pronoun or sb. denoting a person, in cases where the meaning implies more than one, as when the sb. is qualified by a distributive, or refers to either sex: = himself or herself. Cf. THEY 2, THEM 2.

- o 1464 *Rolls of Parlt.* V. 513/2 Inheritements, of which any of the seid persones... was seised by theym self, or joyntly with other.
- o c 1489 CAXTON *Sonnes of Aymon* i. 39 Eche of theym sholde... make theymselfe redy.
- o 1533 MORE *Apol.* 55b, Neyther Tyndale there nor thys precher... hath by theyr maner of expounyng... wonne them self mych wurshyp.
- o 1600 SHAKS. *Lucr.* 125 Euery one to rest themselues [*ed.* 1594 himselfe] betake.
- o 1654-66 EARL ORRERY *Parthen.* (1676) 147 All that happened, which every one assured themselves, would render him a large sharer in the general joy.
- o 1874 DASENT *Half a life* 3 Every one likes to keep it to themselves as long as they can.

- **Their**

3. Often used in relation to a singular sb. or pronoun denoting a person, after *each*, *every*, *either*, *neither*, *no one*, *every one*, etc. Also so used instead of 'his or her', when the gender is inclusive or uncertain. Cf. THEY 2, THEM 2; NOBODY 1b. (Not favoured by grammarians.)

- o 13.. *Cursor M.* 389 (Cott.) Bath ware made sun and mon, Aiper wit þer ouen light.
- o c 1420 *Sir Amadace* (Camden) l, Iche mon in thayre degre.
- o 14.. *Arth. & Merl.* 2440 (Kolbing) Many a Sarazen lost their liffe.
- o 1533 [see THEMSELVES 5].
- o 1545 ABP. PARKER *Let. to Bp. Gardiner* 8 May, Thus was it agreed among us that every president should assemble their companies.
- o 1563 WYNGET *Four Scoir Thre Quest.* liv, A man or woman being lang absent fra thair party.
- o 1641 BEST *Farm. Bks.* (Surtees) 126 Holes, of that bignesse that one may thrust in their neafe.
- o 1643 TRAPP *Comm. Gen.* xxiv. 22 Each Countrey hath their fashions, and garnishes.
- o 1749 FIELDING *Tom Jones* VII. xiv Every one in the House were in their beds.
- o 1771 GOLDSM. *Hist. Eng.* III. 241 Every person... now recovered their liberty.
- o a 1845 SYD. SMITH *Wks.* (1850) 175 Every human being must do something with their existence.
- o 1848 THACKERAY *Van. Fair* xli, A person can't help their birth.

- o 1858 BAGEHOT *Lit. Studies* (1879) II. 206 Nobody in their senses would describe Gray's 'Elegy' as [etc.].
- o 1898 G. B. SHAW *Plays* II. *Candida* 86 It's enough to drive anyone out of their senses.

- Nobody

- b. Followed by *they*, *their*, or *them*.

- o 1548 UDALL, etc. *Erasm. Par. Luke* 94 b, No bodye will receiue you into their house.
- o 1628 tr. *Mathieu's Powerfull Favorite* 108 No body should dare to stretch out their arme, or present their bosome to receiue him.
- o 1704 N. N. tr. *Boccalini's Advts. fr. Parnas.* II. 13 Such Confusion, that no body knew what they were to do, or what to let alone.
- o 1755 WHARBURTON in W. & Hurd *Lett.* (1809) 201 Nobody has yet written against me, but at their own expence.
- o 1831 WHEWELL in *Todhunter Life* II. 112 Nobody will know the origin of pliocene, &c., till you tell them.
- o 1856 F. E. PAGET *Owlet of Owlst.* 9 Nobody likes to be turned out of quarters where they have lived snugly and comfortably for scores of years.
- o 1874 L. STEPHEN *Hours in Library* III. 333 Nobody ever put so much of themselves into their work.

- 10. Everyone

c. *pron.* Everybody; sometimes written as one word. The pronoun referring to *every one* is often *pl.*: the absence of a sing. pron. of common gender rendering this violation of grammatical concord sometimes necessary.

- o 1735 JOHNSON tr. *Lobo's Voy.* 99 Every one Sacrifices a Cow or more, according to their different Degrees of Wealth or Devotion.
- o 1870 DASENT *Eventful Life* (ed. 4) I. 1 Every one had made up their minds that I was to be one thing, and I came out another.
- o 1877 W. H. MALLOCK *New Repub.* (1878) 94 Everyone then looked about them silently in suspense and expectation.



## *The Language Instinct* Steven Pinker (1994)

### Chapter 12: The Language Mavens

Sometimes an alleged grammatical "error" is logical not only in the sense of "rational" but in the sense of respecting distinctions made by the formal logician. Consider this alleged barbarism, brought up by nearly every language maven:

- Everyone returned to their seats.
- Anyone who thinks a Yonex racquet has improved their game, raise your hand.
- If anyone calls, tell them I can't come to the phone.
- Someone dropped by but they didn't say what they wanted.
- No one should have to sell their home to pay for medical care.
- He's one of those guys who's always patting himself on the back. [an actual quote from Holden Caulfield in J. D. Salinger's *Catcher in the Rye*]

They explain: *everyone* means *every one*, a singular subject, which may not serve as the antecedent of a plural pronoun like *them* later in the sentence. "Everyone returned to *his* seat," they insist. "If anyone calls, tell *him* I can't come to the phone."

If you were the target of these lessons, at this point you might be getting a bit uncomfortable. *Everyone returned to his seat* makes it sound like Bruce Springsteen was discovered during intermission to be in the audience, and everyone rushed back and converged on his seat to await an autograph. If there is a good chance that a caller may be female, it is odd to ask one's roommate to tell *him* anything (even if you are not among the people who are concerned about "sexist language"). Such feelings of disquiet -- a red flag to any serious linguist -- are well founded in this case. The next time you get corrected for this sin, ask Mr. Smartypants how you should fix the following:

Mary saw everyone before John noticed them.

Now watch him squirm as he mulls over the downright unintelligible "improvement," *Mary saw everyone before John noticed him*.

The logical point that you, Holden Caulfield, and everyone but the language mavens intuitively grasp is that *everyone* and *they* are not an "antecedent" and a "pronoun" referring to the same person in the world, which would force them to agree in number. They are a "quantifier" and a "bound variable," a different logical relationship. *Everyone returned to their seats* means "For all X, X returned to X's seat." The "X" does not refer to any particular person or group of people; it is simply a placeholder that keeps track of the roles that players play across different relationships. In this case, the X that comes back to a seat is the same X that owns the seat that X comes back to. The *their* there does not, in fact, have plural number, because it refers neither to one thing nor to many things; it does not refer at all. The same goes for the hypothetical caller: there may be one, there may be none, or the phone might ring off the hook with would-be suitors; all that matters is that every time there is a caller, if there is a caller, that caller, and not someone else, should be put off.

On logical grounds, then, variables are not the same thing as the more familiar "referential" pronouns that trigger number agreement (*he* meaning some particular guy, *they* meaning some particular bunch of guys). Some languages are considerate and offer their speakers different words for referential pronouns and for variables. But English is stingy: a referential pronoun must be drafted into service to lend its name when a speaker needs to use a variable. Since these are not real referential pronouns but only homonyms of them, there is no reason that the vernacular decision to borrow *they*, *their*, *them* for the task is any worse than the prescriptivists' recommendation of *he*, *him*, *his*. Indeed, *they* has the advantage of embracing both sexes and feeling right in a wider variety of sentences.

## **APPENDIX B**

### ***Data showing Toleragenic Potential of hES derived Cells***

#### **Example 1**

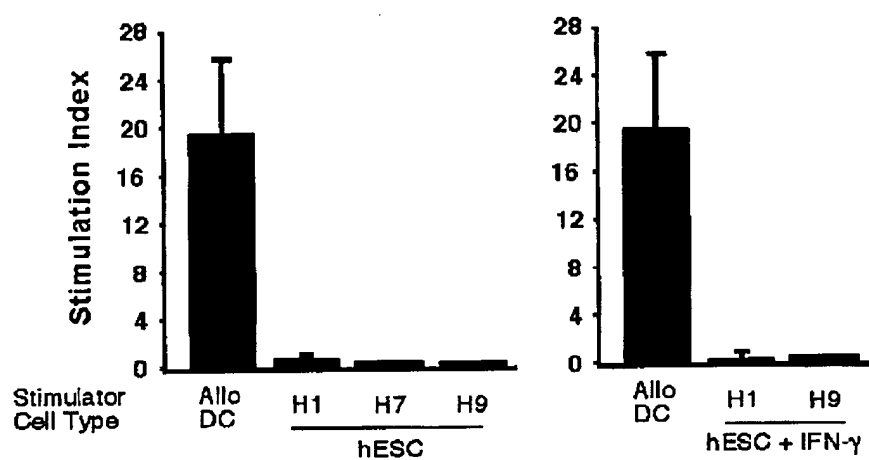
The ability of hES cells to induce proliferation of allogeneic T cells was measured in a mixed lymphocyte reaction (MLR). It was found that hES cell lines are unable to induce allo-reactivity in primary human T cells, even after stimulation with interferon gamma.

Peripheral blood leukocytes were isolated from heparinized blood using a density gradient. To enrich for T lymphocytes, separated cells were incubated for 2 h at 37°C, and the non-adherent cells were collected and frozen for later use. Dendritic cells (DCs) were prepared by culturing the remaining adherent cells for 7 d in medium containing human recombinant GM-CSF and IL-4.

The mixed lymphocyte reaction was performed as follows: stimulator cells were irradiated, and then  $1 \times 10^5$  to  $1 \times 10^2$  cells were plated in 96-well round bottom plates. Responder PBMC or T cells were added at a concentration of  $1 \times 10^5$  per well, and the plates were cultured for 5 days. The wells were then pulsed with [ $^3$ H]thymidine, harvested, and counted.

Figure 1 shows the results of the direct MLR where undifferentiated hES cells were used as stimulators at a 1:10 ratio to responding T cell enriched (monocyte depleted) peripheral blood leukocytes (mean stimulation index  $\pm$  SEM of multiple wells from 3 donors). The positive control are dendritic cells (DC) obtained from an allogeneic donor, which stimulated a strong proliferative response by the T lymphocytes.

However, none of the three hES cell lines tested were able to stimulate T cell proliferation. In contrast to what would be predicted for mature cells like cardiomyocytes, the early stage hES cells do not provoke immune reactivity in allogeneic responder cells.

**Figure 1**

## Example 2

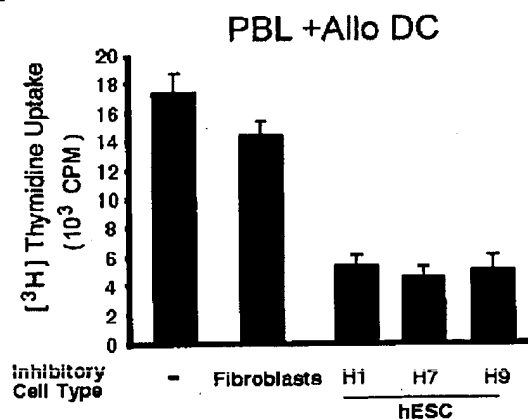
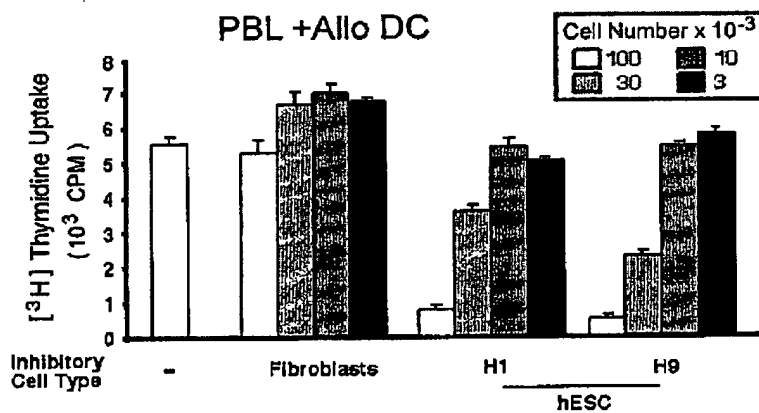
The next experiment shows that hES cells are not just inert and inactive participants — they actively suppress immunoreactivity, even between stimulators and responders that are otherwise highly immunogenic.

Mixed lymphocyte reactions were set up that contained three components: human irradiated PBL stimulator cells, allogeneic human dendritic cell (DC) responders prepared as in the previous example from a different donor, and irradiated modulator cells, being tested for their ability to inhibit the reaction between the PBL stimulators and the DCs. Responder T cells ( $1 \times 10^5$ ) were cultured in combination with  $1 \times 10^5$  irradiated human fibroblasts or hES cells. Subsequently,  $1 \times 10^4$  irradiated dendritic cells were added per well. After 5 days culture, the cells were pulsed with [ $^3\text{H}$ ]thymidine, washed, and counted.

**Figure 2** shows the results (mean  $\pm$  SEM). The PBLs used in this experiment invoked a strong proliferative response to the DCs, as indicated by uptake of tritiated thymidine. Adding BJ fibroblasts into the reaction had no significant effect. However, undifferentiated hES cells of the H1, H7 and H9 lines all showed an ability to quench the reaction to about 1/3 to 1/4 of the control value.

**Figure 3** shows a subsequent experiment in which the inhibitory effect of the hES cells was titrated. Serial reduction in the number of hES cells resulted in a gradual loss of the inhibitory effect, showing that inhibition by hES cells of alloactivation in a mixed lymphocyte reaction is dose-dependent (Panel B). The MLR was inhibited at a hES cell:T cell ratio of 1:1 or 1:3.

This demonstrates that hES cells actually prevent immune cells from reacting against stimulators that otherwise have very strong immunostimulatory capacity.

**Figure 2****Figure 3**

### Example 3

A subsequent experiment illustrates that progenitor cells made from hES cells retain the ability of these cells to prevent stimulation of autologous T lymphocytes.

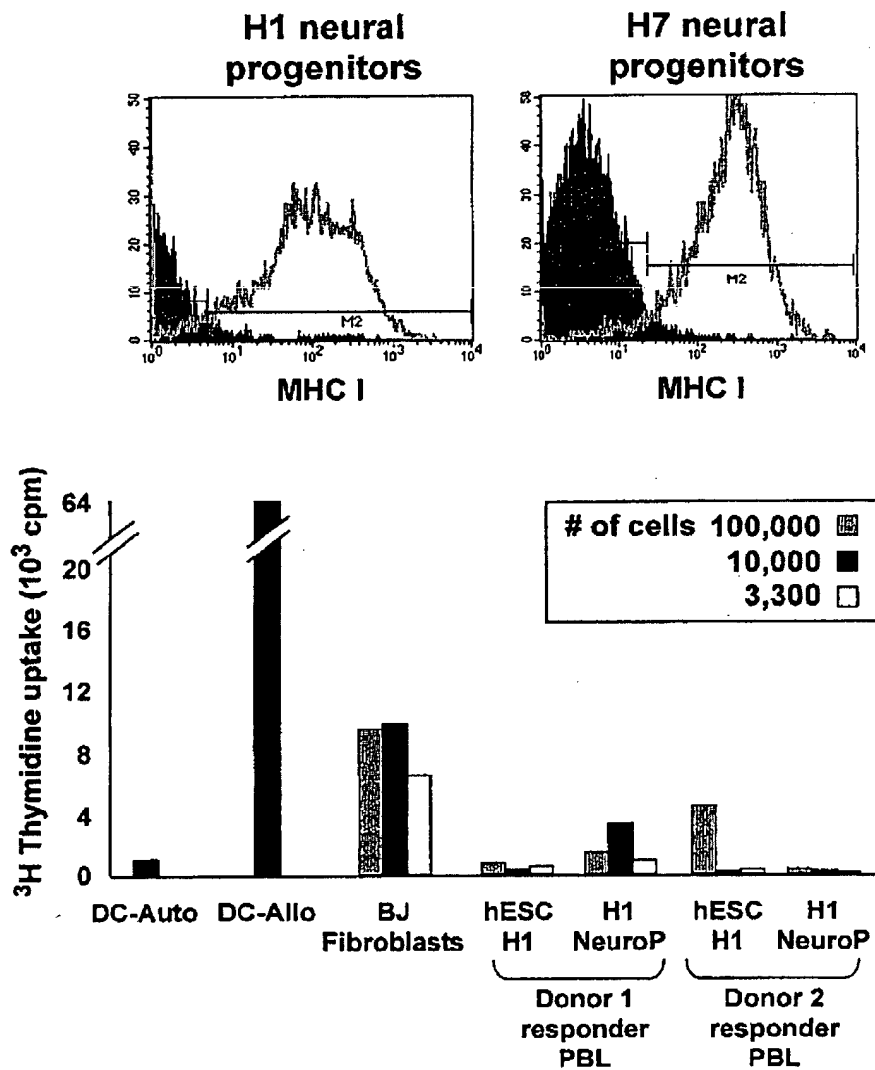
Early stage progenitor cells were obtained by established methods. hES cells were cultured in suspension for 4 days so as to form embryoid bodies. They were plated onto poly-L-lysine/fibronectin-coated plates in a medium containing N2 supplement, B27 supplement, EGF, bFGF, PDGF-AA, and IGF-1, and cultured for 3 days so as to make neural progenitors (WO 03/000868). The cells were harvested by brief trypsinization, plated onto poly-L-lysine, and then cultured in medium containing B27 supplement, NT-3, and BDNF for 5 days. After replating, they were cultured with, BDNF, EGF, and bFGF. They were fed three times per week, and replated every 7 days.

Figure 4 shows MHC Class I expression in the differentiated progenitor cells, evaluated by FACS analysis (Upper panels). Compared with undifferentiated hES cells, the neural progenitor population derived from both hES lines express higher levels of MHC Class I antigens on their surface.

However, this apparent increase in MHC Class I antigen expression in the progenitors did not increase their ability to stimulate allogeneic T cell proliferation (Lower panel). In fact, the hES derived progenitors failed to induce significant T cell proliferation by responder populations from two donors. Undifferentiated hES cells were similarly poor stimulators. In contrast, normal BJ fibroblasts induced moderate levels of T cell proliferation, compared with the dendritic cell positive control.

These results show that toleragenic properties of hES cells apparently persist in progenitor cells during the early stages of differentiation.

**Figure 4**







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**LAST PAGE**